The specification was objected to because of certain formal matters. First, the specification was objected to because of the discrepancy between the labeling of Figure 9 and the description thereof in the Brief Description of the Drawings section. Applicant's hereby proffer an amendment to address that point. Applicants also hereby submit additional copies of Figures 6,7 and 10.

Claims 1 and 21-28 have been rejected pursuant to 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Patent Office has objected to the newly introduced term "intact" as being "unclear". Applicants respectfully disagree. First, as the Examiner notes in the Action, Applicants' use of the term "intact" is consistent with the "common usage of that term." Under the patent law, where the term is clear when given its conventional meaning, no further inquiry is required. Moreover, the term "intact" was clearly understood by the Office and supported by the specification as evident from one of this application's grandparents, U.S. Patent No. 5,010,010 and has consistently been used over 10 years of prosecution. Under the circumstances, there is no doubt as to the clarity of the meaning of "intact" to those of ordinary skill in the art. However, in an effort to advance prosecution on the merits and without agreeing with the Examiner's position, Applicants have amended the claims to remove the word "intact".

The Patent Office has also objected to the use of the terms "substantially equivalent" and "essentially equivalent." The use of the modifiers "substantially" and "essentially" was intended to convey to the reader that the recombinantly produced hPTH of the present invention need not have <u>identical</u> biological activity when compared to naturally occurring hPTH. However, Applicants concede that the term "equivalent," standing alone, can convey that same intention. Therefore, and in an effort to

avoid any possible source of ambiguity, as well as to advance prosecution on the merits, Applicants have amended the claims to remove the terms "substantially" and "essentially" from the appropriate claims.

Finally, with respect to claim 27, the Patent Office has questioned the metes and bounds of the term "fully active in adenylate cyclase assay". Applicants believe that the term is clear and unambiguous to those of ordinary skill in the art. It is the obligation of the Patent Office to provide some evidence or scientific reason to support its assertion. None has been provided. In the absence of same, Applicants respectfully submit that the term is as clear and definite as the subject matter will allow, and understood by those of ordinary skill in the art.

Claims 1 and 21-28 stand rejected pursuant to 35 U.S.C. § 102(b) as allegedly being anticipated by, or in the alternative, pursuant to 35 U.S.C. § 103 as allegedly being obvious in view of *Brewer et al.*, U.S. Patent No. 3,886,132. Applicants respectfully traverse.

In rejecting the claims over *Brewer et al.*, the Patent Office took the position that three incorrect amino acids reported in the sequence of 34 amino acid fragment synthesized by *Brewer et al.* did not defeat *Brewer et al.'s* usefulness as a reference because those errors did not appear to involve the purified, naturally occurring material initially disclosed in *Brewer et al.* The Patent Office went on to note that "[t]he additional arguments pertaining to Brewer are drawn to the *synthetic* peptide of Brewer, and do not address the purified (naturally occurring) protein disclosed by Brewer, upon which this rejection is based." *Official Action* at 7.

What is common to both aspects of the Patent Office's rejection is a misunderstanding of Applicants' past arguments with regard to *Brewer et al.* As will be demonstrated herein,

Applicants were not, and are not, arguing patentability with regard to the synthetic N-terminal fragment produced by *Brewer et al.* Instead, Applicants have argued that the present invention is patentable over the isolated, naturally occurring hPTH discussed by *Brewer et al.*, in column 2 thereof.

First, the Patent Office's position presumes that during the isolation process of *Brewer et al.*, neither sequencing errors nor *in situ* modification could have occurred. Therefore, the only possible source of errors in the N-terminal sequence of the synthetic peptide would be post-isolation errors. While the Patent Office's position in this regard is logical, it is unsupported on the record.

More importantly, whether or not what *Brewer et al.* isolated was hPTH or a modified hPTH, it is clear that *Brewer et al.* did not produce a recombinant hPTH having the purity and attributes of the present invention.

As discussed at column 2, *Brewer et al.* first extracted parathyroid hormone from dried, defatted parathyroid tissue and then fractioned the result. The resulting material was further purified by gel filtration, followed by ion exchange chromatography on a CM-cephadex column employing an ammonium acetate gradient. See, column 2, lines 3-11. *Brewer et al.* suggest that the result is a highly purified naturally occurring hPTH. However, as references cited by the Patent Office, namely *Kimura et al.* and *Kumagaye et al.* clearly demonstrate, *Brewer et al.'s* assertions of purity are little more than a boast.

As Dr. Maggio discussed in paragraph 9 of his previously filed Declaration, FIG. 2 of *Kimura et al.* on page 496 thereof is an HPLC profile of mixture obtained after use of a separation protocol such as that disclosed in *Brewer et al.*, FIG. 2 clearly shows that impurities are evident. Thus the product from the *Brewer et al.* protocol was crude. *Kimura et al.*

demonstrate that the use of a combination of gel filtration and ion exchange chromatography results in an impure product. Thus, *Kimura et al.* prove that when the purification protocol used by *Brewer et al.* is employed on naturally occurring hPTH, a relatively low level purity results.

This conclusion is further dramatized by the fact that *Kimura et al.* added an additional RP-HPLC step to the protocol described by *Brewer et al.* in recognition of the need to obtain better purity. Even with this step wholly absent in *Brewer et al.*, the later reference by *Kumagaye et al.* showed that the purity of product obtained by *Kimura et al.* was insufficient. This only serves to further dramatize the difference between *Brewer et al.*'s unsupported claim to purity and the actual results obtained from the practice of *Brewer et al.*'s separation protocol.

It should be abundantly clear from the foregoing and, indeed, from the references cited by the Examiner, that *Brewer et al.* do not teach or suggest a recombinantly produced hPTH having either the purity or the attributes of the hPTH of the claimed invention. Moreover, the Examiner has already recognized that Applicants have established that different biological properties are associated with the recombinantly made proteins when compared to synthetic analogs disclosed in the references cited in the prior Official Action. The Examiner has also acknowledged that this fact is sufficient to overcome the art relating to chemically synthesized hPTH.

In view of the deficiencies of *Brewer et al.*, and the attributes of the hPTH of the present invention, it is respectfully submitted that the claimed subject matter is novel and unobvious in view of all of the prior art of record. This is particularly true as to claims such as, for example, claims 21,

24, 27 and, in particular, 22 which expressly claim certain biological properties.

Should the Examiner have any questions with regard to the foregoing, she should fee free to contact the undersigned, at her convenience, at (908) 654-5000. Furthermore, should any fee be due and owing in this regard, the Examiner is hereby authorized to charge Applicant's Deposit Account No. 12-1095 therefor.

From the foregoing, further favorable action in the form of a notice of allowance is believed to be next in order, and such action is earnestly solicited.

Respectfully submitted,

LERNER, DAVID, LITTENBERG,
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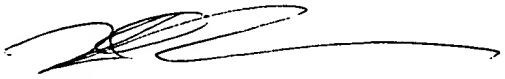

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